Investigation into the Medical, Developmental, and Adaptive Behavior Phenotype of Infants and Toddlers with Williams Syndrome

Undergraduate Research Thesis

Presented in partial fulfillment of the requirements for graduation with *honors research distinction* in the undergraduate colleges of The Ohio State University

by

Rebecca Kirchner

The Ohio State University

May 2015

Project Advisor: Dr. Marilee Martens, Department of Psychology

Abstract

Williams syndrome (WS) is a neurodevelopmental disorder that causes cardiac abnormalities, difficulties eating and sleeping, cognitive delays, and hypersociability. Although researchers have conducted characterizations of children and adults with WS, less is known about younger children with this disorder. This study will characterize the medical, developmental, and adaptive behavior features of infants and children with WS aged 3 months - 5 years. Data for this project was obtained from 16 infants and toddlers who came to the Nationwide Children's Hospital/Nisonger Center Williams Syndrome Clinic from 2007-2014, including parent reported developmental history, medical data, and standardized developmental testing. Thirty-one percent (31.3%) of parents reported that their infant/toddler with WS had sleeping problems and 58.3% reported feeding difficulties. Delays were noted in the acquisition of developmental milestones, particularly in language development. Levels of adaptive behavior were in the Mildly Delayed range. Within the Practical domain of adaptive behavior (Home Living, Community Use, Health and Safety, Self Care), Community Use skills were significantly stronger than Self Care skills. A significant main effect was also found between the three composite scores on the Bayley Scales of Infant and Toddler Development (Motor, Cognitive, and Language), with lower scores appearing in the Motor Domain. The data collected thus far highlights the need for early intervention in these young children.

Investigation into the Medical, Developmental, and Adaptive Behavior Phenotype of Infants and Toddlers with Williams Syndrome

Williams syndrome (WS) is a neurodevelopmental disorder caused by a deletion of approximately 26 genes on chromosome 7 (7q11.23) (Peoples et al., 2000). This rare syndrome affects 1 in 7,500 to 1 in 20,000 individuals (Strømme, Bjørnstad, & Ramstad, 2002; Wang et al., 1997) and can now be genetically confirmed via florescent *in situ* hybridization or microarray analysis (Lowery et al., 1995). Distinctive physical characteristics are evident such as dysmorphic facial features including, but not limited to, broad brows, a puffy area around the eyes, a short upturned nose, and a wide mouth with full lips (Morris & Mervis, 1999). It is very common to observe a hypersensitivity to sound, with younger children becoming extremely startled by noises, and older children and adults seeming to hear certain sounds before others do (Marler, Elfenbein, Ryals, Urban, & Netzloff, 2005). Cardiovascular problems are another very common characteristic of individuals with WS, specifically supravalvular aortic stenosis (a narrowing in the aorta), which occurs in 65-75% of individuals with WS (Morris & Mervis, 1999).

Cognitive delays are also common in individuals with WS, with 75% of young children demonstrating IQ and adaptive behavior scores consistent with a developmental delay, and the remaining 25% exhibiting learning disabilities (Mervis & Klein-Tasman, 2000). In a majority of cases, language is delayed initially, but eventually develops into a strength compared to their visuospatial abilities (dealing with visual perceptions of objects and the spatial relationship between them) and motor skills (Udwin & Yule, 1990). Areas such as auditory memory and language are relatively strong, while motor coordination and numeracy (addition, subtraction, multiplication, division) tend to be less developed (Bellugi, Wang, & Jernigan, 1994). Children

with WS also have a unique behavior profile, which can include the following: attention seeking behaviors, difficulties with eating and sleeping, anxiety, and poor relationships with peers (Davies, Howlin, & Udwin, 1997). However, individuals with WS are extremely sociable, and often display an outward lack of fear towards strangers as well as overfriendliness (Jones et al., 2000).

Medical Profile

Williams syndrome is accompanied by numerous medical issues, which can affect many different body systems and present as early as infancy. Individuals with WS are smaller than average, with 70% of a 42-person sample having a birth length and weight less than the 10th percentile on a normal growth curve (Morris, Demsey, Leonard, Dilts, & Blackburn, 1988). The short stature seen in individuals with WS can be linked to several factors, such as restricted prenatal growth, failure to thrive early in life, restricted growth in childhood, and advanced puberty (Martin, Smith, Cole, & Preece, 2007). Infantile hypercalcemia, or an abnormally high level of calcium in the blood, is also common in WS, and can contribute to extreme irritability, constipation and vomiting (Martin, Snodgrass, & Cohan, 1984). As previously mentioned, heart abnormalities are extremely common, particularly supravalvular aortic stenosis. Stenosis of the central or peripheral pulmonary arteries, although less common, is observed as well (Pober and Dykens, 1996). The exact etiology of these vascular abnormalities is unknown, but is most likely due to the hemideletion of the elastin gene. Many individuals with WS also have high blood pressure throughout their lifespan, with the risk of hypertension resulting from the vascular abnormalities (Pober and Dykens, 1996). Gastrointestinal problems are prevalent as well, with reported feeding problems in 70% of infants (Morris et al., 1988). A failure to thrive has also been reported in the majority of infants (80%), most likely due to a combination of feeding

difficulties, vomiting, colic, and constipation (Morris et al., 1988). Sleep deregulation is also considered a common feature of individuals with WS. Up to 97% of parents reported that their child with WS shows resistance going to bed, has trouble going to sleep, or has frequent awakenings at night (Annaz, Hill, Ashworth, Holley, & Karmiloff-Smith, 2011).

Developmental/Cognitive Profile

Individuals with WS are found to have a very specific cognitive profile, which includes a much higher than expected level of auditory rote memory (memorization of sounds by repetition), and language ability only slightly higher than expected, with receptive language abilities usually a strength in comparison to expressive language abilities (Brock, 2007). A thorough review was conducted in order to further understand the developmental and cognitive features of individuals with WS (Martens, Wilson, & Reutens, 2008). Martens and colleagues reviewed 178 published studies and summarized the developmental and cognitive profile of individuals with WS. Based on this review, the average IQ of WS individuals ranged from 40-100, with an average Full Scale IQ of 55. In regard to their language development, children with WS displayed an extensively larger expressive vocabulary than similar-aged children with Down syndrome, but had significantly lower scores in comparison to chronological age-matched typically developing (TD) children (Mervis & Robinson, 2000).

Greer and colleagues investigated the cognition/intelligence of children with WS ranging in ages from 4-18 years (Greer, Brown, Pai, Choudry, & Klein, 1997). Cognitive skills ranged from the Moderate range of intellectual ability (Full Scale IQ 40-55), to within the lower limits of the Low Average range (Full Scale IQ 70-85). Fifty-three percent (53%) of children and adolescents with WS displayed intellectual skills within a Mildly Delayed range (Full Scale IQ

55-70) (Greer et al., 1997). It is important to note that while a large age range was encompassed for this study, children under the age of four years were not included in the sample.

While a fair amount of research has been conducted on children, adolescents, and adults with WS, much less research has been focused on the infant/toddler age range. There is evidence that developmental milestones are delayed, with walking occurring on average at 21 months, talking at 26 months, and toilet training at 39 months (Morris et. al, 1988). Toddlers and young children with WS have a higher level of verbal skills in relation to their visuospatial construction abilities (seeing an object in parts, and then creating a replica from the parts). Using the Bayley Scales of Infant Development (Bayley, 1969), Mervis & Bertrand (1997) found that infants and toddlers overall passed more verbal questions than non-verbal items, and demonstrated extreme difficulties with tasks relating to visuospatial construction. In the area of cognition, they found nearly all infants and young children with WS displayed a developmental delay.

Adaptive Behavior Profile

Adaptive behavior can be defined as the learned conceptual, social, and practical skills that are performed by individuals in their day-to-day lives (Schalock et al., 2011). These skills are closely tied with intellectual disabilities as significant limitations in adaptive behavior, coupled with significant limitations in intellectual functioning and an age of onset before 18, operationally defines an intellectual disability (Tassé et al., 2012).

Children with WS demonstrate deficits in adaptive behavior, according to parental reports using the Vineland Adaptive Behavior Scales, Interview Edition (Greer et al., 1997; Sparrow, Balla, & Cicchetti, 1984). Greer and colleagues found that 40% of children and adolescents with WS had overall Adaptive Composite Scores in the Moderately Deficient range (40-55), 33% scored within the Mildly Deficient range, (55-70) and 27% scored in the Moderately Low range

(70-85). Communication and Socialization skills appeared more developed than Daily Living Skills, and no gender differences were found (Greer et. al., 1997). In regard to overall strengths and weaknesses within the adaptive behavior domains, heterogeneity is evident, with no one overall area identified as a significant strength or weakness (Brawn & Porter, 2011).

Another, more specific study was conducted concerning the adaptive behavior skills of four through eight-year-old children with WS (Mervis, Klein-Tasman, & Mastin, 2001). The results, gathered from the Vineland Adaptive Behavior Checklist, Interview Edition, showed strengths in Socialization skills, as well as a strength in Communication skills in comparison to Daily Living skills. The Motor Skills of the four- and five-year-old children were characterized, and the results showed a significant weakness in Motor Skills relative to the other areas. Upon further analysis using age equivalent scores, the researchers found that overall adaptive behavior showed a significant increase as a function of chronological age. Although young children with WS showed a weaker level of adaptive behavior than expected for their chronological age in all categories, this delay did not increase between the ages of four to eight years. Again, it is important to note for the purposes of the current study, that children under the age of four years were not included in the above-mentioned study.

Current Study

As the literature demonstrates, there has been a substantial amount of research investigating the medical, developmental, and adaptive behavior characteristics of individuals with WS, but significantly less is known about the subpopulation of infants and toddlers. Furthermore, there has been little research encompassing all three of these domains in one project. This is the first study to assess the adaptive behavior of WS infants and toddlers using the Adaptive Behavior Assessment System, 2nd ed. (ABAS-2) (Harrison & Oakland, 2003). As

stated by the American Association on Intellectual and Developmental Disabilities (AAIDD), an intellectual disability is characterized by significant limitations in both adaptive behavior and intellectual functioning, occurring before the age of 18. The AAIDD defines adaptive behavior as is the collection of conceptual, social and practical skills that individuals need to function in their daily lives. The domains of the ABAS-2 (Conceptual, Social, and Practical) follow the AAIDD guidelines for measuring adaptive behavior, in contrast to the Communication, Daily Living Skills, and Socialization domains utilized in the Vineland Adaptive Behavior Scores, Second edition, which has been used in previous studies. This research will characterize the overall medical, developmental, and adaptive behavior phenotype of infants and toddlers with WS, as well as examine any strengths or weaknesses in the profiles of these young children that may point to specific areas of needed intervention.

Method

Participants

The participants in this study were 16 individuals (nine females, seven males) aged 3 months to 65 months (M=28.7 months, SD=19.3 months) who attended the Williams Syndrome Clinic at Nationwide Children's Hospital in Columbus, OH from 2007-2014. In order to be eligible for this study, participants had to be under the age of six years when they were first seen by the clinic. Five additional individuals within this age range were excluded from the study due to incomplete data on the intake form (n=3) or because the children also met criteria for an Autism Spectrum Disorder (n=2). Data for this study comes from paperwork completed by the child's primary caregiver, as well standardized evaluations given while the individuals were at the Clinic. The only required component for participants was a consent form signed by their

parent or guardian, giving permission for their confidential records to be used for research.

Materials

Adaptive Behavior Assessment System, Second Edition. The Adaptive Behavior Assessment System, Second Edition (ABAS-2), completed by the child's primary caregiver, was used to assess the child's personal and social skills necessary for daily living (Gray & Carter, 2013). The test form utilized in this study was designed for individuals from birth through 5 years, 11 months. The ABAS-2 measures adaptive behavior in three domains: Conceptual, Social, and Practical, and provides a General Adaptive Composite Score. The domains, along with the General Adaptive Composite, have a mean score of 100, and a standard deviation of 15. The three domains are each divided into ten sections, including: Communication, Community Use (e.g. "finds the restroom in a public place"), Functional Pre-Academics (e.g. "counts three or more objects"), Health and Safety, Home/School Living, Leisure (e.g. "plays with a single toy or game for at least one minute") Self-Care (e.g. "opens mouth when offered food on a spoon") Self-Direction (e.g. "entertains self in crib or bed for at least one minute after waking"), Social (e.g. "smiles when he/she sees a parent") and Motor. These skill areas have a mean of 10 and a standard deviation of 3. It is important to note that when the child is under the age of one year, the Community Use, Functional Pre-Academics, and Home Living skill areas are not included in the computation of the adaptive behavior scores. The ABAS-2 uses a rating form to answer how often the child correctly completes the behavior in question when needed without help, unless otherwise indicated. The ratings are based on a 4-point Likert-type scale ranging from 0-3; with 0 meaning that the child is not able to perform the listed behavior, and 3 being the child is always or almost always able to perform the behavior when needed. Reliability studies of the ABAS-2

display evidence of a high degree of internal consistency, with most of the skill area consistency coefficients appearing at .90 or greater.

Bayley Scales of Infant and Toddler Development, Third Edition. The Bayley Scales of Infant and Toddler Development evaluate a child in three areas: Cognitive, Language, and Motor (Michalec, 2011). This test was designed for children from birth-four years. The Cognitive section assesses processing of information, reasoning abilities, memory and habituation skills, and play skills. The Language section is further divided into two areas: Receptive and Expressive. The Receptive section includes discriminating between sounds in a child's environment, as well as understanding and responding to requests. Expressive language is evaluated by a child's ability to name objects and actions, answer questions, use sentences containing more than one word, as well as communicate his/her wants. The motor skills section contains both fine motor (grasping objects, reaching objects, visual tracking) and gross motor (jumping, balance, and locomotion) skill components. The Cognitive, Language, and Motor scales have a mean of 100 and a standard deviation of 15, while the subtests (such as Receptive Communication or Gross Motor) have a mean of 10 and a standard deviation of 3. The Bayley Scales of Infant and Toddler Development is an active assessment, in which the child must complete tasks as explained by the examiner. The Bayley Scales of Infant and Toddler Development, Third edition, exhibit strong reliability, with domain composites ranging from .91-.93, and reliability of subtest composites ranging from .86 to .91.

Williams Syndrome Intake Form. The Williams Syndrome Intake Form (see Appendix A) was given to the parents or guardians of each child upon their first visit to the Williams Syndrome Clinic. The Nisonger Center developed this form in order to receive necessary information about the child upon their first visit. Parents or guardians of the child completed all

sections to the best of their knowledge. The information asked on the form is as follows: child's full name and birthday, parent contact information, pregnancy information, age and method of WS diagnosis, history of feeding difficulties, persistent and/or past health problems, sleep difficulties, hearing and vision test results, medications, developmental milestones, and a description of attention and behavior.

EPIC online charting system. EPIC was utilized in order to record patient medical information. In order to ensure confidentiality and preserve HIPPA regulation, a secure remote access ID was provided by Nationwide Children's Hospital via a remote access chip. The EPIC online charting system includes all patient information, including, but not limited to, height/weight information, genetic, urinalysis, and blood testing results, summaries of patient visits, and any pertinent data from other medical professionals.

Procedures

Each participant was given a unique identification number in order to preserve his/her confidentiality. For the data collection, Williams Syndrome Clinic Intake forms were first transferred from handwritten paper copies into an electronic database using Microsoft Access. Although all intake data was transferred, the only data used for the current study was as follows: Birthdate, sleep and/or feeding difficulties, use of a special diet, evidence of hyperacusis (heightened sensitivity to certain sounds), and developmental milestones. If all developmental milestones were not complete at the time of the visit, primary caregivers were contacted to gather the missing information. Standardized testing data was also transferred, including adaptive behavior profiles (ABAS-2), and a developmental assessment (Bayley Scales of Infant and Toddler Development, Third Edition). Patient medical records were accessed via a secure remote access chip to EPIC. This data included blood work, height, and weight. Each child's

height-for-age and weight-for-age percentile was calculated using the British Williams syndrome growth chart, based on the most recent height/weight data collected from individuals with WS (Martin et al., 2007). EPIC records also allowed for the collection of eight of the children's height-for-age and weight-for-age percentiles on a typically developing growth chart. As some children did not have height/weight listed on EPIC, and EPIC's growth chart starts at two years, the remaining eight were calculated by hand. This was done by hand plotting the child's age and height/weight on a copy of the typically developing growth chart. It is important to note that not all variables included responses for the entire sample. Certain variables do not have full sample participation for reasons such as: parents skipping the question, records not being faxed over from other hospitals, or incomplete assessments.

Results

Medical

The distribution of the height-for-age and weight-for-age on the WS growth chart was normally distributed, with 43.8% of the children falling below the 50th percentile in height (Figure 1) and 50% of the children falling below the 50th percentile in weight (Figure 2). On the typically developing growth chart, 50% of the children scored below the 5th percentile in height, and 56.3% scored below the 5th percentile in weight.

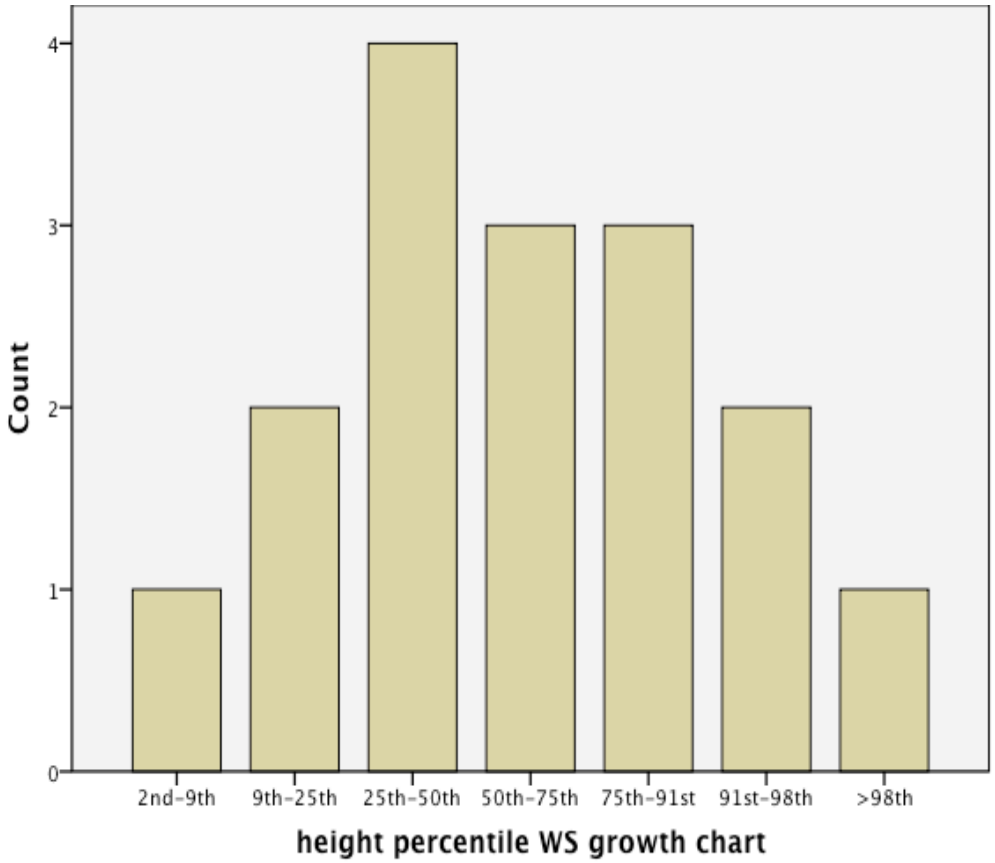

Figure 1. Bar graph displaying number of WS individuals that fell within specific ranges on the WS height-for-age growth chart.

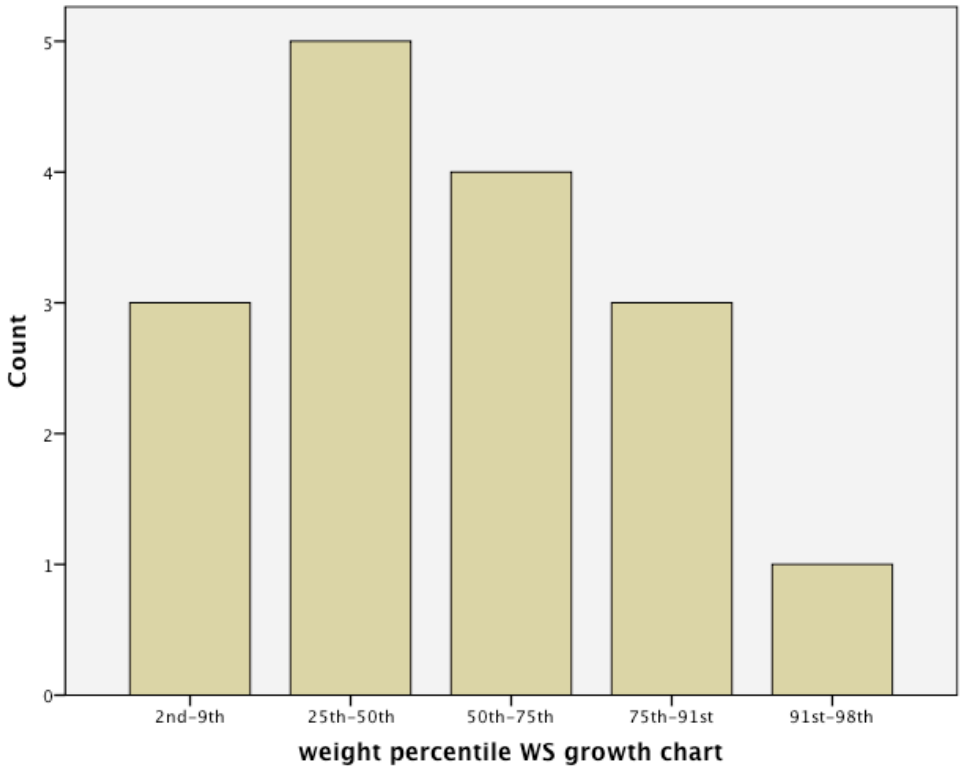

Figure 2. Bar graph displaying number of WS individuals that fell within specific ranges on the WS weight-for-age growth chart.

As high calcium levels and heart abnormalities are both common features of WS, both were assessed; calcium levels via lab results, and heart abnormalities via parental report. Normal calcium levels are dependent on varying characteristics such as age and gender therefore, the levels for the purposes of this study are described as "less than the average range" "within the average range" and "greater than the average range," with the range being the healthy level of each variable in question. The majority of the lab results were found to be within the healthy range, with only three children having elevated calcium levels. No children had levels lower than the normal range. Eight parents reported that their child had a history of heart abnormalities, the most common being a form of stenosis (n=6).

Developmental/Cognitive

In the area of development, WS infants and toddlers reached virtually all of their developmental milestones later than their typically developing peers, with the greatest delay (compared to typically developing children) appearing in the emergence of phrases (Figure 3).

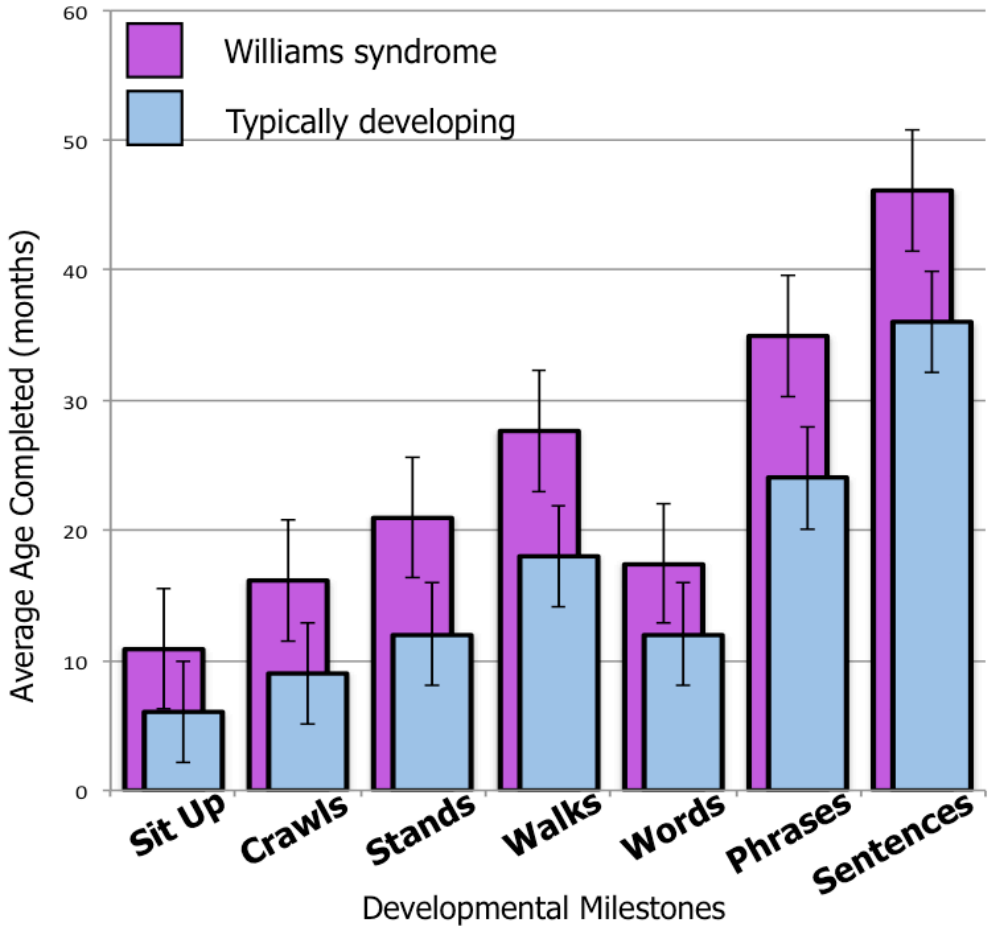

Figure 3. Bar graph displaying average age, in months, that WS infants and toddlers completed specific developmental milestones in comparison to typically developing individuals (data taken from CDC).

The parent-reported intake forms indicated issues with sleeping and eating, as anticipated. Thirty-one percent (31.3%) of parents reported that their infant/toddler had sleeping

problems, 58.3% reported feeding difficulties, and 35.7 % reported that their infant/toddler needed a special diet.

A majority of parents also reported that their child avoided, was attracted to, or was afraid of certain sounds. Forty-six percent (46%) reported that their child avoided certain sounds, 46% reported that their child was attracted to certain sounds, and nearly 54% reported that their child avoided certain sounds.

Table 1 displays the average Bayley Scales scores for language (*M*=74.33, *SD*=10.76), cognition (*M*=71.40, *SD*=13.73), and motor abilities (*M*=65.50, *SD*=7.35). These results demonstrate delays in all areas, with WS children scoring at least one standard deviation below the mean in each domain.

Table 1

Average Scores on the Bayley Scales of Infant and Toddler Development

	N	Mean	Std. Deviation
Bayley Cognitive Composite	10	**71.40**	13.729
Bayley Language Composite	12	**74.33**	10.756
Bayley Receptive Communication	12	6.33	2.348
Bayley Expressive Communication	12	5.17	1.899
Bayley Motor Composite	8	**65.50**	7.348
Bayley Fine Motor	10	4.80	1.751
Bayley Gross Motor	8	3.87	1.727

Given that only seven participants had scores on all three domains of the Bayley Scales, a non-parametric Friedman Test was utilized to compare the three domain scores. The results of the Friedman Test indicated that there was a statistically significant difference across the three

domains (Language, Cognition, and Motor) ($\chi^2 = 8.07$, $p = .018$). Inspection of the median values showed that the Language domain ($Md = 79$) was the highest-scoring domain. A Wilcoxon Signed Rank Test revealed that the language domain score ($Md = 79$) was significantly higher than the motor domain score ($Md = 67$), $z = -2.37$, $p = .018$, with a large effect size ($r = .63$). A Paired-Sample T-Test displayed that within the Language domain, Receptive Language was significantly higher than Expressive Language ($M = 1.167$, $t = 2.382$, $p = .036$).

Adaptive Behavior

Table 3 displays the average mean scores for the measure of adaptive behavior (ABAS-2). Again, delays were observed in all areas, with the overall level of adaptive behavior appearing within the Mildly Delayed range (M=62.50, SD=11.83).

Table 3.

Average Scores on the ABAS-2

	N	Mean	Std. Deviation
General Composite	15	**64.00**	10.549
Conceptual Domain	15	**68.47**	12.472
Communication	15	5.13	2.560
Functional Academics	11	5.09	2.119
Self-Direction	15	5.20	2.678
Social Domain	15	**71.93**	11.793
Leisure	15	5.67	2.820
Social	15	5.53	2.356
Practical Domain	15	**67.93**	11.585
Community Use	11	5.18	1.662
Home Living	11	5.00	2.569
Health and Safety	15	5.47	2.774
Self Care	15	3.67	1.952

The average strengths and weaknesses within each of the ABAS-2 skill areas are displayed in Figure 4. These were determined by identifying scores significantly higher or lower than other scores within that same domain (domain being either Conceptual, Social, or Practical), based on a protocol provided by the authors of the ABAS-2. Heterogeneity was found, with no single area appearing as an overall strength or weakness. A repeated measure ANOVA between the three ABAS-2 adaptive behavior domains (Conceptual, Social, and Practical) indicated a significant main effect (F= 2.162; p=.155; ηp^2=.25). A repeated measures ANOVA was also utilized to compare scores on the skill areas within each of the three ABAS-2 adaptive behavior domains. No significant difference was found within the Conceptual or Social domains, but a significant main effect was noted between the skill areas within the Practical domain (Home Living, Community Use, Health and Safety, Self Care) (F = 9.67, p = .005, ηp^2=.78). An examination of pairwise comparisons indicated that scores in Community Use were significantly higher than scores in Self Care (p = .006). Figure 5 displays the means of the Practical domain skill areas, showing difference between means.

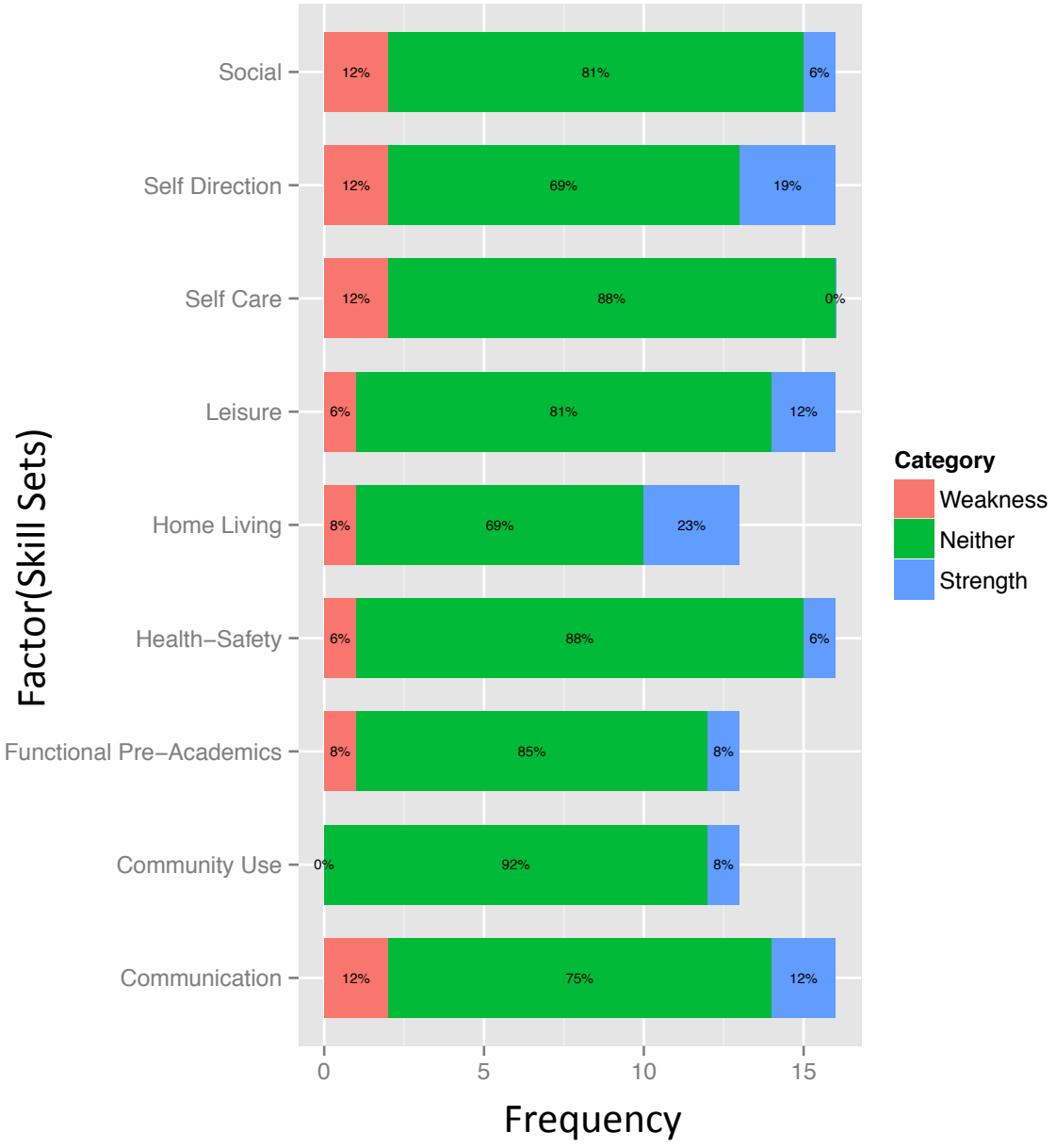

Figure 4. Graph displaying percentages of participants that displayed a relative strength, weakness, or neither, across skill sets. Home Living, Functional Pre-Academics, and Community Use skill sets do not include participants under the age of one year.

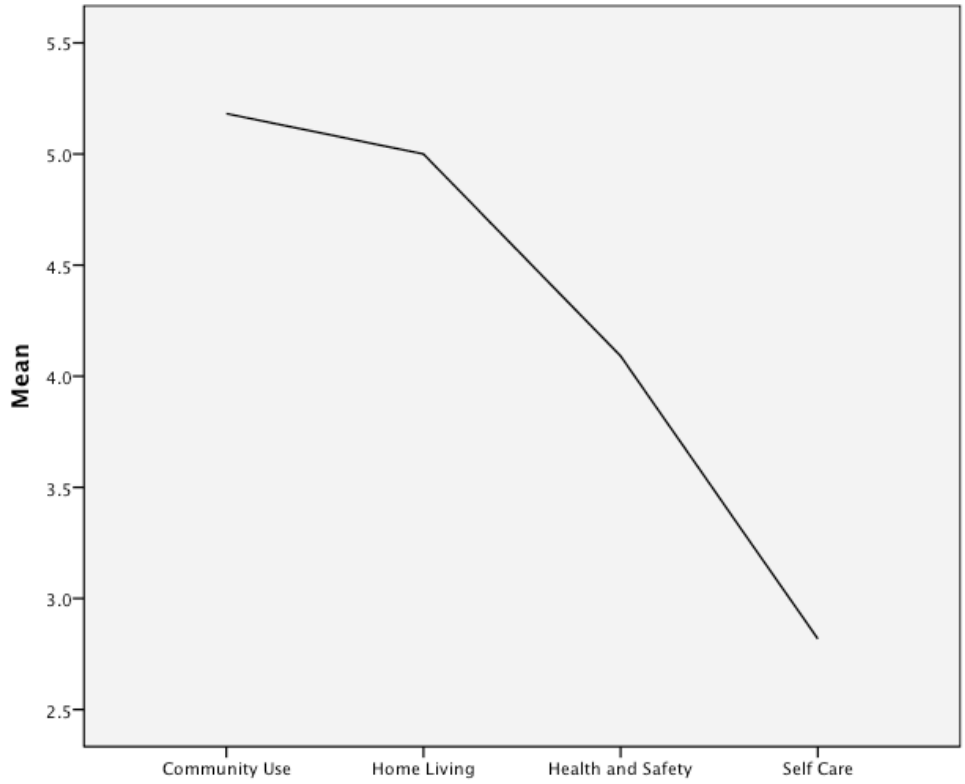

Figure 5. Line graph displaying ABAS-2 skills areas within the Practical domain.

Using the handbook provided by the authors of the ABAS-2, a mental test age was computed for each child for each of the skill areas. For each skill area, the child's mental test age was then correlated with their chronological age. A significant positive correlation was found between each skill area and chronological age. The strongest correlations came from the Communication, Community Use, and Motor skill sets, with the correlations being $r = .942$, $r = .949$, and $r = .962$, respectively. There was a negative correlation (-.499, $p = .049$) between the ABAS General Composite standard score and chronological age, suggesting that the gap between typically developing children and those with WS is widening between the ages of infancy and five years.

Discussion

The aim of this study was to characterize the overall medical, developmental, and adaptive behavior characteristics of infants and toddlers with WS. This is the first study to utilize the ABAS-2 in the characterization of adaptive behavior in WS, and the findings point to skill areas that can be targeted for intervention.

Medical

In relation to the EPIC charting data, fewer children than expected exhibited high levels of calcium. This low value (*n*=3) was unexpected, as abnormally high calcium is common in WS individuals (Martin et al., 1984). For comparison, a study by Morris et al. (1988), found that 67% of infants exhibited hypercalcemia. However, the generalizability of Morris and colleagues' findings remains uncertain, as their sample included only six individuals. This could be a question that is investigated in future research with a larger sample size. Another potential area of future research would be to examine correlations between developmental assessment scores and calcium levels, as high calcium can cause irritability, and it is a possibility that this could affect the validity of testing results.

Using a growth curve generated from Martin et al. (2007), the infants/toddlers in the current study exhibited an overall normal distribution for height-for-age, and a positively skewed distribution for weight-for-age. When initially looking at the EPIC data to discover where each child appeared on a weight-for-age and height-for-age percentile chart, it became apparent that the formula EPIC was using to calculate these percentiles must be incorrect. For example, individuals with WS are shorter than average in stature, so it was impossible for a child to be 16.32% for height on a WS chart, and 16.58% on a typically developing chart. This issue has

been sent to the EPIC headquarters, as this is most likely affecting many hospitals. We are awaiting confirmation that this problem has been resolved.

Generating height and weight percentiles from the research of Morris et al. (1988) was also not feasible, as the percentiles are separated into 2 SD below the mean, at the mean, and 2SD above the mean, versus percentile rankings. The Morris and colleagues' growth chart also had not been updated since 1988 and their sample included only 109 individuals from infancy through 20 years. This highlights the need for new WS growth charts that not only encompass a larger sample and more recent data, but one that is more useful to parents. This can be achieved by modeling the WS growth chart created using British children with WS, which separates the percentile groups by ranges, similar to the TD growth charts (Martin et al., 2007).

Developmental/Cognitive

Developmentally, children with WS reached their developmental milestones later than their TD peers, similar to what was found by Morris et al. (1988). However, the children in the current sample learned to walk approximately six months later than those in the Morris et al. sample. However, this could be attributed to the small sample size in the current study, as only 11 of the individuals in our sample had began to walk, in comparison the 42-person sample obtained by Morris and colleagues.

Surprisingly, fewer parents than expected reported problems with eating and sleeping in their child, as well as avoiding, being afraid of, or being attracted to certain sounds. Previous studies have found up to 97% of parents reporting that their child has difficulties falling or staying asleep, 71% experiencing feeding difficulties, and 84% of parents reporting that their child had mild-moderate hyperacusis (Annaz, Hill, Ashworth, Holley, Marmiloff-Smith, 2011; Morris et al., 1988;). In comparison, this study found just 31% of parents reporting that their

child had sleeping difficulties, 58.3% reporting feeding difficulties, and an average of 42.5% of parents reporting that their child avoided, was afraid of, or was attracted to certain sounds. The low number of parents reporting that their child avoided, was afraid of, or was attracted to certain sounds could be due to the fact that the current sample included four infants under the age of one year, and it may be difficult for a parent to determine if their infant is avoiding or attracted to certain sounds at this age. Further research is needed to investigate prevalence of sleeping, eating, and hyperacusis in WS, as these issues are extremely difficult for both the child and their families. Although unlikely, if the Nisonger Center/Nationwide Children's Hospital clinic patients truly are experiencing this issues less frequently than others with WS, more research is needed to determine the causes, and how this decrease in symptoms can be brought to the rest of the population.

Scores on the Bayley Scales of Infant and Toddler Development were at least one standard deviation below the mean across all all areas. These delays were expected, as mild-moderate cognitive delays are common in individuals with WS (Mervis & Klein-Tasman, 2000). It was also expected that language skills would be significantly higher than motor skills, as reported by Mervis & Bertrand (1997) and Mervis & Robinson (2000). Previous studies with WS have shown that Receptive Language is usually a relative strength in comparison to Expressive Language (Mervis, Robinson, Rowe, Becerra, & Klein-Tasman, 2003), and this study obtained similar results. However, there is very little research using the Bayley Scales as a measure of cognitive development, most likely due to the limited research conducted within this age group. It is also important to note that neither of the previously listed studies used the third edition of the Bayley Scales, as this edition was released in 2005. Previous additions of the Bayley did not include a language domain, and instead included communication as a component

of the mental domain. Furthermore, the communication component was not further separated into Expressive and Receptive Language. More research is needed measuring cognitive ability in WS infants and toddlers using the Bayley Scales of Infant and Toddler Development in order to offer a more thorough comparison to our current study.

Adaptive Behavior

On the ABAS-2, deficits were noted across all domains and skill sets, as found in previous studies (Greer et al., 1997; Sparrow et al., 1984). However, it is important to note that all of the previous adaptive behavior research utilized the Vineland Adaptive Behavior Scales. No known study looking at WS infants and toddlers has used the ABAS-2, and further research is needed in order to achieve a more detailed comparison. In the area of strengths and weaknesses of Adaptive Behavior, no specific area was found to be an overall strength or weaknesses, similar to the heterogeneity previously reported **(**Brawn & Porter, 2014).

The specific main effect found within the Practical domain and subsequent pairwise comparison displaying Community Use scores as significantly higher than Self-Care scores verifies an area in need of future research. Due to the fact that the ABAS-2 is a relatively new assessment and therefore was not used in previous research, it is important to determine if these results are due to the small sample size of this study, or if they can be generalized to the overall WS infant and toddler population. However, it is important to note that concurrent validity is supported with moderate-to-strong correlations between the ABAS-2 and other measures of adaptive behavior, such as the Vineland (Lopata et al., 2012). Future research is needed to discern if these results can be duplicated, with further investigation into the cause of the low Self-Care scores. It is possible that the scores are significantly lower on this skill set as the first eight questions relate to sleeping and eating behaviors (questions such as “swallows liquids with

little to no difficulty" or "sleeps through most of the night, waking no more than one or two times"). Although these problems were not highly reported in the current study, it is possible that the sleeping and eating issues common to WS infants and toddlers contributed to the low Self-Care scores. It is also a possibility that in the young infant/toddler population, parents are choosing to do more for their child, which is causing some of these skills to develop at a slower rate.

The significant positive correlation found between each individual's mental test age and chronological age on the ABAS-2 is similar to what has been found in previous studies in 4-8 year old children (Mervis et al., 2001). In the WS infant and toddler population, adaptive skills are increasing significantly as a function of chronological age, with no skills hitting a 'plateau' of no improvement. The negative correlation between the ABAS Composite standard score and chronological age suggests that the gap between WS infants and toddlers and typically developing infants and toddlers continues to grow between the ages of infancy and five years. This finding is not surprising, as few demands are placed on infants. However, as infants grow older, more is expected of them and this is where delays become more evident. However, this decline does not seem to continue as the child ages, as previous research with four to eight-year-old children found no correlation between standard score and chronological age on the Vineland (Mervis et al., 2001). Future research should investigate this relationship using the ABAS-2 with older children.

Conclusion

The findings in the current study are similar to previous studies concerning WS children, suggesting that the delays displayed in WS children begin as early as infancy. Further research is needed to create a more robust profile of WS infants and toddlers. Additional research

utilizing the Bayley Scales of Infant and Toddler Development, Third Edition and the ABAS-2 is needed as well, as little research has included these assessments. The problems with the EPIC charting system need to be resolved to ensure that parents are receiving accurate growth information about their child, and future research is needed in order to update the WS growth chart. Further research is needed in order to determine potential reasons behind the low scores in Self-Care, and future interventions that may help with this skill. The current study highlights the need for early intervention in these young children across all areas of development, and calls for many areas in need of future research.

References

Annaz, D., Hill, C. M., Ashworth, A., Holley, S., & Karmiloff-Smith, A. (2011). Characterisation of sleep problems in children with Williams syndrome. *Research in Developmental Disabilities, 32(1), 164-169*.

Bayley N. (1969). *Bayley Scales of Infant Development*. New York: Harcourt Assessment

Bayley, N. *Bayley Scales of Infant and Toddler Development*. 3rd ed. (2006). San Antonio TX: Harcourt Assessment

Bellugi, U., Wang, P. P., & Jernigan, T. L. (1994). Williams syndrome: An unusual neuropsychological profile. In S. H. Broman & J. Grafman (Eds.), *A typical cognitive deficits in developmental disorders: Implications for brain function* (pp. 23-56). Hillsdale, NJ: Lawrence Erlbaum.

Brawn, G., & Porter, M. (2014). Adaptive functioning in Williams syndrome and its relation to demographic variables and family environment. *Research in Developmental Disabilities, 35(12), 3606-3623*.

Brock, J. (2007). Language abilities in Williams syndrome: A critical review. *Development and Psychopathology, 19*(01), 97-127.

Davies, M., Udwin, O., & Howlin, P. (1998). Adults with Williams syndrome: Preliminary study of social, emotional, and behavioural difficulties. *British Journal of Psychiatry, 172*, 273–276.

Greer, M. K., Brown, F. R. III, Pai, G., Choudry, S. H., & Klein, A. J. (1997). Cognitive, adaptive, and behavioral characteristics of Williams syndrome. *American Journal of Medical Genetics, 74*, 521–525.

Gray, Sarah A. O. & Carter, A. S. (2013). Adaptive Behavior Assessment

System, Second Edition (ABAS-II) In F. Volkmar (Ed.), *Encyclopedia of autism spectrum disorders* (pp. 52–55). Berlin, Germany: Springer-Verlag

Harrison, P., & Oakland, T. (2003). *Adaptive Behavior Assessment System (ABAS-II).* San Antonio, TX: The Psychological Corporation.

Jones, W., Bellugi, U., Lai, Z., Chiles, M., Reilly, J., … Adolphs, R. (2000). Hypersociability in Williams syndrome. *Journal of Cognitive Neuroscience, 12,* 30-46.

Lopata, C., Fox, J. D., Thomeer, M. L., Smith, R. A., Volker, M. A., Kessel, C. M., ... & Lee, G. K. (2012). ABAS-II ratings and correlates of adaptive behavior in children with HFASDs. *Journal of Developmental and Physical Disabilities*, *24*(4), 391-402

Lowery, M., Morris C., Ewart, A., Brothman L., Zhu X, Brothman, A. (1995). Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients. *American Journal of Human Genetics,* 57(1), 49.

Marler, J. A., Elfenbein, J. L., Ryals, B. M., Urban, Z. & Netzloff, M. L. (2005). Sensorineural hearing loss in children and adults with Williams syndrome. *American Journal of Medical Genetics, 138A,* 318-327.

Martens M. A., Wilson, S. J., & Reutens, D. C. (2008). Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry, 49*, 576-608.

Martin, N.D., Snodgrass, G. J., and Cohen, R. D. (1984). Idiopathic infantile hypercalcaemia--a continuing enigma. *Archives of Disease in Childhood, 59,* 605-613.

Martin, N. D., T., Smith, W. R., Cole, T. J., & Preece, M. A. (2007). New height, weight, and head circumference charts for British children with Williams syndrome. *Archives of Disease in Childhood, 92,* 598-601.

Mervis, C. B., & Bertrand J. (1997). Developmental relations between cognition and language: Evidence from Williams syndrome. In L. B. Adamson & M.A. Romski (Eds.), *Communication and language acquisition: Discoveries from atypical development* (pp. 75-106). Baltimore: Paul H. Brookes.

Mervis, C. B., & Klein-Tasman, B. P. (2000). Williams syndrome: Cognition, personality, and adaptive behavior. *Mental Retardation and Developmental Disabilities Research Reviews, 6*, 148–158.

Mervis, C. B., Klein-Tasman, B. P., & Mastin, M. E. (2001). Adaptive behavior of 4- through 8-year-old children with Williams syndrome. *American Journal on Mental Retardation, 106*, 82–93.

Mervis, C. B., & Robinson, B. F. (2000). Expressive vocabulary ability of toddlers with Williams syndrome or Down syndrome: A comparison. *Developmental Neuropsychology, 17*, 111–126.

Mervis, C. B., Robinson, B. F., Rowe, M. L., Becerra, A. M., Klein-Tasman, B.P. (2003). Language Abilities of Individuals with Williams Syndrome. *International Review of Research in Mental Retardation, 27,* 35-81.

Michalec, D. (2011) Bayley Scales of Infant Development: Third Edition. In S. Goldstein & Jack Naglieri (Eds.) *Encyclopedia of Child Behavior and Development* (pp. 215).

Morris, C. A., & Mervis, C. B. (1999). Williams syndrome. In S. Goldstein, & C.R. Reynolds, (Eds), *Handbook of neurodevelopmental and genetic disorders in children* (pp. 555–590). New York: Guilford Press.

Morris, C.A., Demsey, S. A., Leonard, C. O., Dilts, C., & Blackburn, B. L. (1988). Natural history of Williams syndrome: Physical characteristics. *Journal of Pediactrics, 113,* 318-326.

Peoples, R., Franke, Y., Wang, Y., Perez-Jurado, L., Paperna, T., Cisco, M., & Francke, U. (2000). A physical map, including a BAC/PAC clone contig, of the Williams–Beuren syndrome deletion region at 7q11.23. *American Journal of Human Genetics, 66*, 47–68.

Pober, B. R. & Dykens, E. M. Williams syndrome: An overview of medical, cognitive, and behavioral features. (1996). *Child and Adolescent Psychiatric Clinics of North America, 5(4), 929-943*.

Schalock, R. L., Borthwick-Duffy, S. A., Bradley, V. J., Buntinx, W. H. E., Coulter, D. L., Craig, E. M., . . . Yeager, M. H. (2010). Intellectual disability: Diagnosis, classification, and systems of supports (11th ed.). Washington, DC: American Association on Intellectual and Developmental Disabilities.

Sparrow, S.S., Balla, D.A., & Cicchetti, D.V (1984). *Vineland Adaptive Behavior Scales, Interview Edition* [Measurement instrument]. Circle Pines, MN: American Guidance Service.

Strømme, P., Bjørnstad, P.G., & Ramstad, K. (2002). Prevalence estimation of Williams syndrome. *Journal of Child Neurology, 17*, 269–271.

Tassé, M. L., Schalock R. L., Balboni, G., Bersani, H., Borthwick-Duffy, S. A., Spreat, S., . . . Zhang, D. (2012). The construct of adaptive behavior: Its conceptualization, measurement, and use in the field of intellectual disability. *American Journal of Intellectual and Developmental Disabilities, 117*(4), 291-303.

Udwin, O., & Yule, W. (1990). Expressive language of children with Williams

syndrome. *American Journal of Medical Genetics, 6*, 108–114.

Wang, Y. K., Samos, C. H., Peoples, R., Perez-Jurado, L. A., Nusse, R., & Francke, U. (1997). A novel human homologue of the *Drosophilia frizzled* wnt receptor gene binds wingless protein and is in the Williams syndrome deletion at 7q11.23. *Human Molecular Genetics, 6*, 465–472.

Appendix A

Nationwide Children's Hospital/Nisonger Center Williams Syndrome Clinic Intake Form

Williams Syndrome Clinic
INTAKE FORM

Email completed form to:
Rachel.lambert@osumc.edu

OR

Mail completed form to:
Attn: Rachel Lambert
Nisonger Center, McCampbell Hall
1581 Dodd Dr.
Columbus, OH 43210

Health and Development History

Date

Child's Full Name | Date of Birth

Your Full Name(s) | Relationship to Child

Telephone (Home) | (Work)

Email Address | (Cell)

Home Address

Name of School | Grade

School Address

School IEP Team – Name and Title

Primary Care Provider (i.e. pediatrician, family practitioner, nurse practitioner):

In addition to yourself, to whom would you like the report sent? (primary care provider) Please include the address.

Please list the question(s) you would like answered once the evaluation is completed:

1. _____

2. _____

3. _____

4. _____

Whose idea was it that your child have an evaluation? _____

Birth History

Which of the mother's pregnancies was this? (1st, 2nd, etc.)? _____

Has the mother had miscarriages? ☐ Yes ☐ No Previous premature baby(ies)? _____

During pregnancy *(please check Yes or No if the following occurred. If Yes, please describe briefly)*

☐ Yes ☐ No Illness/infection/accident Describe: _____

☐ Yes ☐ No Medication taken Describe: _____

☐ Yes ☐ No Smoking If yes, how much: _____

☐ Yes ☐ No Alcohol intake If yes, how much: _____

☐ Yes ☐ No Drug intake If yes, how much: _____

Weight gain in pounds (during pregnancy): _____

Length of pregnancy in weeks (most babies are born between 38-42 weeks): _____

Labor

☐ Yes ☐ No Induced

☐ Yes ☐ No Lasted over 12 hours

Delivery

☐ Yes ☐ No Caesarean section

☐ Yes ☐ No Anesthesia If yes, what type: ☐ Spinal ☐ Epidural ☐ General (asleep)

☐ Yes ☐ No Complications If yes, describe _____

Newborn

Birth weight: _____ Cried right away: ☐ Yes ☐ No

Apgar scores, if known: _____ 1 minute _____ 5 minutes

☐ Yes ☐ No Complications — If yes, describe: _____

☐ Yes ☐ No Breast fed — If yes, how long?: _____

Went home after _____ days in the hospital

Infancy

☐ Yes ☐ No Enjoyed cuddling

☐ Yes ☐ No Fussy, irritable — Comments: _____

☐ Yes ☐ No More active than others _____

Diagnosis

Age at which child was diagnosed with Williams Syndrome _____

FISH (fluorescence *in situ* hybridization) test used to confirm? ☐ Yes ☐ No

Who did FISH testing? _____

History of Infancy, Childhood and Adolescence

A. Immunization record: ☐ Up to date

☐ Some immunizations not given. Please explain:_____

_____

B. Childhood diseases (age or N/A):

Mumps _____ Measles _____

German Measles _____ Chicken Pox _____

Roseola _____ Whooping Cough _____

Scarlet Fever _____ Meningitis/Encephalitis _____

C. Check other problems child has now or has had in the past:

	Now	Past		Now	Past
Recurrent stomach aches	_____	_____	Pneumonia or Bronchitis	_____	____
Urine problems	_____	_____	Persistent vomiting	_____	____
Frequent constipation	_____	_____	Persistent diarrhea	_____	____
Seizures	_____	_____	Headaches	_____	____

Recurrent infections	_____	_____	Dizziness	_____	____
Ear infections	_____	_____	Unconsciousness	_____	____
Accidents (head injuries, other injuries, broken bones?)	_____	_____	Asthma	_____	____
Unusual movements	_____	_____	Tics	_____	____

C. If you checked any of the previous problems, please describe further:

Other problems not included in the above list (please specify) _____
Do you have any concerns about your child's size or growth?

☐ Yes ☐ No If *yes,* please describe:

Does your child have a heart abnormality?

☐ Yes ☐ No If *yes,* please describe:

Does your child have any other physical disability or impairment?

☐ Yes ☐ No If *yes,* please describe:

If female and past puberty, age when period (menstruation) began _____

Do you have any concerns about your child's sexual development? _____

D. Does your child have any known allergies or sensitivities to food or drugs? ☐ Yes ☐ No ☐ Do not know

If *yes*, please explain: _____

E. Does your child have any problems associated with going to bed or sleeping? ☐ Yes ☐ No ☐ Do not know

If *yes*, please explain: _____

Is your child currently taking any medication or has he/she received prescribed medication (for a month or longer) in the past?

☐ Yes ☐ No

If *yes*, please answer the following:

Medication	Amount taken per day	Is the child still taking medication? ☒ Yes	No	Why is/was it taken?

17. Is there a history on either side of the child's family of conditions such as birth defects, diabetes, seizures, mental retardation, mental or emotional disorders, childhood hearing loss, or learning disabilities?

☐ Yes ☐ No ☐ Do not know

If *yes*, please explain:

Growth and Development

Does your child have any feeding difficulties?

☐ Yes ☐ No If *yes*, please explain:

List any foods that are avoided:

Does your child receive any special foods, formulas, vitamins, dietary supplements, or is he/she on a special diet?

☐ Yes ☐ No If *yes*, please explain:

Has your child's vision ever been tested?

☐ Yes ☐ No ☐ Do not know

If *yes*, what were the results? If no, do you have concerns?

Who conducted the testing?

Name_____

When was the testing done? _____

Has your child's hearing ever been tested?

☐ Yes ☐ No ☐ Do not know

If *yes*, what were the results? If no, do you have concerns?

Who conducted the testing?

Name_____

When was the testing done? _____

Hyperacousis

1. Does your child avoid certain sounds? ☐ Yes ☐ No
2. Is your child attracted to certain sounds? ☐ Yes ☐ No
3. Is your child afraid of certain sounds? ☐ Yes ☐ No

Explain:

Developmental History

	Age	Not Yet Developed
Sat without support		
Crawled		
Stood without support		
Walked without assistance		
Threw ball		
Spoke first words		
Said phrases		
Said sentences		
Showed clear hand preference		
Bowel trained		
Bladder trained, day		
Bladder trained, night		
Rode tricycle		
Rode bicycle (without training wheels)		
Tied shoelaces		
Named colors		
Named coins		

SIBLINGS

Name	Age	Any medical, social, academic, speech problems?

Play / Leisure Time

How and with whom does your child like to spend his/her play or leisure time?

How much supervision does your child need during play time?

☐ Total Supervision ☐ Some Supervision

☐ A great deal of supervision ☐ Almost no supervision

Family Life

Are there family circumstances that seem to have had a positive effect on your child's development, such as support from relatives, outside activities, etc.?

☐ Yes ☐ No ☐ Do not know

If *yes*, please explain:

Activity, Attention, Behavior

Please check appropriate column	**Not True**	**Sometimes True**	**Very/Often True**
1. Fails to finish things he/she starts			
2. Can't concentrate, can't pay attention for long			
3. Can't sit still, restless, or hyperactive			
4. Fidgets			
5. Daydreams or gets lost in his/her thoughts			
6. Impulsive or acts without thinking			
7. Has difficulty following directions			
8. Talks out of turn			
9. Messy work			
10. Is inattentive, is easily distracted			
11. Talks too much			
12. Fails to carry out assigned tasks			
13. Disturbs other children			
14. Demands must be met immediately			

Please check appropriate column	**Not True**	**Sometimes True**	**Very/Often True**
15. Is easily frustrated			
16. Cries often and easily			
17. Mood changes quickly and drastically			
18. Has temper outbursts, is explosive			
19. Head bangs			
20. Rocks in bed			
21. Is self-destructive			
22. Is difficult to comfort			
23. Is stiff/rigid			
24. Exhibits looseness/floppiness			
25. Is shy with strangers			
26. Is shy with peers			
27. Shows extreme reaction to noise			
28. Has difficulty keeping to schedule or schedule changes			
29. Has difficulty getting satisfied			
30. Fails to be affectionate towards parents			
31. Is cruel to animals			
32. Tics (excessive movements/odd sounds)			

Describe your child's personality – moods, relationships, behavior:

_____

_____

_____

Describe your child's strengths:

Please add any additional information which you feel may help us better understand your child: